REMARKS

Reconsideration of the application is respectfully requested. Claims 1-10 and 13-110 are pending in the application. Claims 3, 6, 7, 13, 15, 16, 36-50, 57-62, 69-98, and 108-110 have been withdrawn from consideration. Therefore, the only claims at issue are claims 1, 2, 4, 5, 8-10, 14, 17-35, 51-56, 63-68, and 99-107.

Claims 1, 22, 33, 54, 55, and 107 have been amended. Claim 1 has been amended to remove the term "optionally" from step (c) and to specify the optical purity of the isolated enantiomer(s) as being at least 90% ee. Support for this amendment is found in the specification at, for example, page 7, line 27 to page 8, line 2. Claims 54 and 55 have been amended to specify that the claimed mutants and variants have an amino acid sequence that is more than 60% identical to the parent amino acid sequence. Support for this amendment is found in the specification at, for example, page 17, line 27 to page 18, line 4. Claims 22, 33, and 107 have been amended to depend from pending claim 2.

New claim 111 has been added. Support for new claim 111 is found in the specification at, for example, page 21, lines 16-28; and page 23, lines 1-12.

No new matter has been added.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 1, 54, and 55 have been rejected under 35 U.S.C. §112, first paragraph, as lacking written description support with respect to the step of selective enzymatic acylation. According to the Examiner, this step is not adequately described because the specification does not disclose any specific enzymatic acylations using an acylating agent, and does not specify how mutants and variants of *Pseudomonas sp.* lipoprotein lipase act as a source of hydrolase enzyme for use in enzymatic acylation.

The rejection is traversed, and reconsideration is respectfully requested.

First, the present specification provides an extensive and detailed description of how enzymatic acylation is carried out according to the present invention. Numerous acylating agents of

formulae (IIIa), (IIIb), and (IIIc) are disclosed (p. 9, line 1 to p. 12, line 22), including vinyl butyrate (p. 11, lines 8-11). The specification also specifies the position on the formula (II) diol where acylation occurs (namely, the primary hydroxyl group; p. 2, lines 14-18), and states that selective enzymatic acylation is performed according to the invention "under conditions substantially suppressing hydrolysis" (p. 13, lines 15-18). Suitable solvents that may be used for this acylation step are also disclosed (p. 13, line 20 to p. 14, line 10), such as organic acids, organic bases, and tertiary amines that improve selectivity (p. 14, line 28 to p. 16, line 9). The specification also discloses various concentrations of the formula (II) diol and acylating agent (p. 14, lines 12-17), and suitable temperatures for the reaction (p. 18, lines 28-29).

Enzymes for use in the claimed acylation are disclosed as well, both generally and specifically – e.g., a hydrolase enzyme, such as a lipase, esterase, acylase, or protease (p. 16, lines 11-12), and numerous exemplary enzymes, including *Pseudomonas sp.* lipoprotein lipase, *Candida antartica* lipase B, Novozyme® 435, and LipoZyme™ TL IM (p. 17, lines 8-20; p. 18, lines 6-23) may be used. The specification also provides various amounts of enzyme that can be used in the reaction (p. 18, lines 31-32).

Furthermore, while it is not necessary to disclose a working example of an enzymatic acylation to satisfy the written description requirement, *see* MPEP §2164.02; *In re Strahilevitz*, 668 F.2d 1229, 1232 (CCPA 1982), the specification nevertheless discloses several examples. More specifically, and contrary to the Examiner's assertion, the specification indeed discloses an enzymatic acylation using an acylating agent because Example 1 describes enzymatic acylation of a diol of formula (II) (i.e., 4-[4-dimethylamino-1-(4'-fluorophenyl)-1-hydroxybutyl]-3-hydroxymethylbenzonitrile) using the acylating agent vinyl butyrate and the immobilized enzyme Novozyme® 435 (p. 49, lines 5-34). Additionally, Example 9 describes enzymatic acylations of the same Example 1 diol using one of several acylating agents (i.e., vinyl acetate, vinyl propionate, vinyl butyrate, vinyl caproate, *n*-butyric anhydride, *iso*-valeric anhydride, or *iso*-butyric anhydride) and Novozyme® 435 (p. 55, lines 5-14; Table 8).

Additionally, regarding the "mutants and variants" recited in claims 54 and 55, these claims have been amended to specify that the mutants and variants have an amino acid sequence that is more than 60% identical to the parent amino acid sequence. The specification discloses that

enzymes equivalent to the parent enzyme may be obtained, for example, by isolating various strains of *Pseudomonas*, *Candida*, or *Thermomyces*, or mutating the DNA encoding the parent enzymes (e.g., to achieve a new amino acid sequence that is more than 60% identical to the parent amino acid sequence). *See* Specification at p. 17, line 27 to p. 18, line 4. The specification also functionally limits the equivalent enzymes called for in claims 54 and 55 to those that are capable of performing the selective enzymatic acylation of the invention. Hence, these disclosures would have led one of ordinary skill in the art to conclude that the inventors were in possession of mutants and variants of *Pseudomonas sp.* lipoprotein lipase, *Candida antartica* lipase B, and *Thermomyces lanuginosus* lipase, including those called for in the present claims.

Given the foregoing, claims 1, 54, and 55 have sufficient written description support because the specification, and particularly the above-described portions, would have led one of ordinary skill in the art to conclude that the inventors were in possession of the full scope of the claimed methods, including the step of selective enzymatic acylation as well as the claimed mutants and variants. Therefore, Applicant respectfully requests that this rejection be withdrawn.

Rejections Under 35 U.S.C. §103

Claims 1, 2, 4, 5, 8-10, 14, 17-35, 51-56, 63-68, and 99-107 have been rejected under 35 U.S.C. §103 as obvious over U.S. Patent No. 4,943,590 ("Boegesoe") in view of U.S. Patent No. 6,551,806 ("Sturmer") and U.S. Patent No. 5,219,743 ("Takano"). Boegesoe is cited by the Examiner as disclosing a reaction scheme in which a racemic diol reacts with an enantiomerically pure acid derivative, after which HPLC separation is used to isolate the corresponding enantiomer of the acid-derived intermediate. The Examiner acknowledges that Boegesoe does not teach either enzymatic acylation with a hydrolase enzyme to prepare the S- or R-diol of formula (II) or the solvent of the present invention. Sturmer is cited by the Examiner as disclosing enzyme-containing polymers used for enantioselective acylation of alcohols, wherein hydrolases such as esterases, lipases, and proteases are identified as suitable enzymes. Takano is cited by the Examiner as disclosing a method for optical resolution of Corey lactone diols using an acylating agent in the presence of an enzyme and any organic solvent that does not inactivate the enzyme. From this, the

Examiner concludes that it would have been obvious to prepare the claimed S- or R-diol by subjecting Boegesoe's racemic diol mixture to selective enzymatic acylation using an acylating agent and an enzyme and any suitable solvent because such a method involves known compounds and a known chemical process that would allegedly yield predictable results.

Claim 1 has been amended to remove the term "optionally" from step (c), thus requiring the step of isolating the recited enantiomer(s), and to specify the optical purity of the isolated enantiomer(s) as being at least 90% ee. Consequently, claims 1, 2, 4, 5, 8-10, 14, 17-35, 51-56, 63-68, and 99-107 are not obvious over Boegesoe, Sturmer, and Takano because the cited references would not have allowed one of ordinary skill to reasonably predict that selective enzymatic acylation could successfully yield the claimed enantiomer(s) with such high purity.

First, Boegesoe does not teach a process of isolating an S- or R-diol from its racemic mixture, but instead discloses the use of a racemic diol to make an S- or R-ester derivative that can be converted to S- or R-citalopram (Boegesoe: cols. 3-4). Boegesoe does not disclose a reaction in which a single enantiomer of a starting diol remains unconverted. Boegesoe also makes no mention of enzymatic acylation.

Additionally, the presently claimed formula (II) diol has a significantly different and more complicated structure than any starting substrate disclosed in Sturmer (*see, e.g.*, 1-phenylethanol shown in Example 2 at col. 14, lines 40-67). Since chemical reactions are generally known to be unpredictable, one of ordinary skill would not have reasonably predicted that Sturmer's process could selectively acylate one of the enantiomers of a formula (II) racemate, let alone yield an enantiomer that could be isolated with an optical purity of at least 90% ee. As described in the specification, separating an acylated enantiomer of formula (IV) from a non-acylated enantiomer of formula (II) is difficult due to the similarity of their structures (*see* p. 21, lines 16-21). The inventors' "intensive investigations," however, led them to discover a successful way to not only selectively acylate an individual enantiomer, but also isolate the unconverted enantiomer to a high degree of purity. *See* Specification at p. 2, lines 14-18; p. 7, line 27 to p. 8, line 2; and p. 21, lines 23-28. The disclosure in Sturmer is insufficient to have led one of ordinary skill to reasonably predict that an enantiomer of the complicated structure of formula (II) could be both selectively isolated and highly purified by the claimed process of selective enzymatic acylation.

Moreover, Takano does not disclose separation of enantiomers from a racemic mixture, but instead discloses a mixture of two different diol enantiomers having different molecular formulae (Takano: col. 4, line 55 to col. 5, line 10). This mixture reacts with an acylating agent and enzyme, yielding an esterified form of one enantiomeric molecule and leaving the other enantiomeric molecule unchanged. Takano would not have led one of ordinary skill to predict how, or even if, enzymatic acylation could be used to selectively acylate one enantiomer in a racemic mixture, as called for in the pending claims, particularly because it is much more difficult to separate opposing enantiomers of a single molecule than those of two different molecules. Thus, Takano fails to cure the deficiencies of Boegesoe and Sturmer.

Given the foregoing, claims 1, 2, 4, 5, 8-10, 14, 17-35, 51-56, 63-68, and 99-107 are not obvious over Boegesoe, Sturmer, and Takano; and Applicant respectfully requests that this rejection be withdrawn.

Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining, which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

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